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L4 L3 and cd40

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(antigen\$ or immunogen\$)same(target\$ or enhanc\$ or deliver\$)

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13 L1

END OF SEARCH HISTORY

L3: Entry 28 of 135

File: PGPB

May 8, 2003

DOCUMENT-IDENTIFIER: US 20030086922 A1

TITLE: METHOD OF PROMOTING AN IMMUNE RESPONSE WITH A BISPECIFIC ANTIBODY

Summary of Invention Paragraph:

[0006] Snider et al, J. Immunol. (1987) 139:1609-16 first described using bispecific antibodies to target an antigen to an Fc receptor on an antigen-presenting cell in an in vitro system. This study used antibody heteroaggregates containing an antibody against a protein antigen covalently crosslinked to an antibody against a target structure on the surface of the antigen presenting cells. Antigen presentation was assessed by measurement of lymphokine released by antigen specific T cell hybridomas. Enhanced presentation occurred when antigen was targeted to MHC class I and class II molecules, surface immunoglobulin, or Fc.gamma. receptors on the surface of a murine B cell lymphoma/hybridoma. The ability of each crosslinked antibody to enhance presentation paralleled the total amount of each that bound to the surface of the antigen presenting cells. This research also found that the presentation of one antigen using crosslinked antibody did not result in enhanced presentation of a second, bystander antigen.

Summary of Invention Paragraph:

[0010] Snider et al, J. Exp. Med. (1990) 171:1957-63, first reported that bispecific antibody targeting of antigen to an Fc receptor on an antigen presenting cell (APC) in mice resulted in enhanced immunogenicity of the antigen in the mice. Bispecific antibodies were prepared by chemically crosslinking an antibody with specificity to hen egg lysozyme (HEL) to various other antibodies, including an antibody to Fc.gamma.III, and anti-I-A, and anti-IgD, each specific for a particular APC cell surface component. This study showed that heterocrosslinked bispecific antibodies, when administered once with nanogram amounts of antigen, in the absence of adjuvant, induced high titers of antibody in mice, and primed mice for a secondary IgG antibody response when rechallenged with soluble antigen.

L3: Entry 106 of 135

File: USPT

Feb 15, 2000

DOCUMENT-IDENTIFIER: US 6024963 A

TITLE: Potentiation of immunogenic response

Brief Summary Text (5):

Another procedure for achieving potentiation is to conjugate the weakly-immunogenic material to a strongly-immunogenic material and administer the conjugate in a vaccine. For example, a conjugate of the capsular polysaccharide of Haemophilus influenzae type b to diphtheria toxoid, as described in U.S. Pat. Nos. 4,496,538 and 4,619,828, or a conjugate of a weak antigen to a monoclonal antibody targeting antigen-presenting cells, as described in

Entry 107 of 135

File: USPT

Jan 4, 2000

DOCUMENT-IDENTIFIER: US 6010902 A

TITLE: Antibody heteroconjugates and bispecific antibodies for use in regulation of lymphocyte activity

Detailed Description Text (5):

Without being bound by theory, it is believed that the heteroconjugates and bispecific antibodies described herein, when reacted with lymphocytes, act by binding to their respective antigens on the surface of the cell, bringing those antigens into close proximity to each other, a step that may mimic the coclustering that occurs, for example, between the T cell receptor and CD4 upon contact of helper T cells with antigen-presenting cells during T cell activation [see, e.g., Kupfer et al., "Coclustering Of CD4 (L3T4) Molecule With The T-Cell Receptor Is Induced By Specific Direct Interaction Of Helper T Cells And Antigen Presenting Cells", Proc. Nat'l. Acad. Sci. USA. 84:5888 (1987)]. This interaction between T cell antigens and the cell surface appears to enhance CD3/Ti-mediated transmembrane signalling and thus T cell activation.

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END OF SEARCH HISTORY

Summary of Invention Paragraph:

[0034] * antigen CD40 and mannose receptor with a mean intensity of 50 to 500,

Summary of Invention Paragraph:

[0062] As example of other chemical ligands interacting with mononuclear cells and allowing differentiation into MD-APCs, one may cite detoxified LPS such as lipid A, C3 and other ligands of complement receptors, taxols, oxydoreductors such as flavenoids or polyphenols, ligands to CD40, to the TNF receptors or to vitamin D3 receptors.

Summary of Invention Paragraph:

[0078] or bispecific antibodies targeting on the one side, a surface antigen or a surface receptor of the MD-APCs and, on the other side, a relevant antigen against which an immune response is desired.

Summary of Invention Paragraph:

[0083] As example of other chemical ligands interacting with mononuclear cells and allowing differentiation into MD-APCs, one may cite detoxified LPS such as lipid A, C3 and other ligands of complement receptors, taxols, oxydoreductors such as flavenoids or polyphenols, ligands to CD40, to the TNF receptors or to vitamin D3 receptors.

Summary of Invention Paragraph:

[0098] The invention also relates to bispecific antibodies liable to recognize an antigen of a MD-APCs of the invention and an antigen of a tumoral cell or of a pathogen which is to be targetted to said MD-APCs.

Summary of Invention Paragraph:

[0105] * antigen CD40 and mannose receptor with a mean intensity of 50 to 500,

Summary of Invention Paragraph:

[0115] with GM-CSF, 500 U/ml chemical ligands interacting with mononuclear cells and allowing differentiation into MD-APCs, such as detoxified LPS such as lipid A, C3 and other ligands of complement receptors, taxols, oxydoreductors such as flavenoids or polyphenols, ligands to CD40, to the TNF receptors or to vitamin D3 receptors; as example of ligands, histamine (10.sup.-4 M), cimetidine (10.sup.-6 M) or another H.sub.2 antagonist of histamine, or with histamine, cimetidine in the absence of any exogenous cytokines. Endogenous cytokines are released by mononuclear cells stimulated by ligands.

Summary of Invention Paragraph:

[0122] In order to obtain specific cellular vaccine, it is also possible at the end of the differentiation stage of the macrophage culture to add bispecific antibodies targeting a membrane antigen, or a surface receptor of MD-APCs on one side and the relevant antigen on the other side.

Detail Description Paragraph:

[0179] As example of other chemical ligands interacting with mononuclear cells and allowing differentiation into MD-APCs, one may cite detoxified LPS such as lipid A, C3 and other ligands of complement receptors, taxols, oxydoreductors such as flavenoids or polyphenols, ligands to CD40, to the TNF receptors or to vitamin D3 receptors.

Detail Description Table CWU:

5TABLE 5 It gathers a complete phenotypic characterization of MD-APCs recovered after 6 days of culture according to the invention (analysis by flow cytometry). Phenotype % Cells Mean fluo intensity
CD45 97.6 CD14 6.8 172 CD3 13 CD19 15 CD56 3.8 CD4-PE 95 CD25 1.7 CD45RO 99 CD16 1.8 31

CD32 63 163 CD64 4 12 CD1a 31 216 CD1c 58 505 CD83 9 18 HLA-DR 99 266 HLA-I 99.6 582
CD40 98 991 CD80 78 64 CD86 99 744 IgG1-FITC 6.7 11 IgG1-PE 20 (16) 55 IgG1-Cy5 19 (29) 50
IgG2a-FITC 5.3 19 IgG1 i 1.6 75 IgG2a i 3.8 21 IgG2b i 3.2 15

CLAIMS:

1. A method of clinically treating a patient, comprising: administering to said patient an effective amount of monocyte derived antigen presenting cells (MD-APCs) which present the following properties: the presence on the MD-APC cell surface of surface antigens CD80 and CD86, and the presence on the MD-APC cell surface of surface antigens CD40 and mannose receptor.

10. The method according to claim 8, wherein said MD-APCs present surface antigens CD40 and mannose receptor on their surface.

15. A method of clinically treating a patient, comprising: administering to said patient an effective amount monocyte derived cells (MD-APCs) which present the following properties: the presence on the MD-APC cell surface of surface antigens CD80 and CD 86, the presence on the MD-APC cell surface of surface antigens CD40 and mannose receptor, and the presence on the MD-APC cell surface of surface antigen CD 14.

DOCUMENT-IDENTIFIER: US 20020102278 A1

TITLE: CELLULAR VACCINES AND IMMUNOTHERAPEUTICS AND METHODS FOR THEIR PREPARATION

Summary of Invention Paragraph:

[0012] In summary, the method of the invention involves the steps of (1) treating weakly- or non-immunogenic autologous cells (target cells) in order to amplify primary and costimulatory T cell activation signals in the cells, and (2) attaching to the treated cells a substance capable of binding to one or more antigens on the treated cells and to one or more T cell activation costimulatory molecules on the surface of T cells (such as CD28), thereby providing the treated cells with the capacity to physically link to T cells and to activate the costimulatory signal. Such substances include, but are not limited to, bispecific monoclonal antibodies (Bi-MAbs) targeted to antigen on the treated cells and to CD28 and/or other costimulatory molecules on T cells. The first step may be skipped when the autologous cell is attached with (1) a bridge molecule with two or more binding sites for T cell activation costimulatory molecules on the surface of T cells, or (2) two or more bridge molecules each with one or more binding sites for T cell activation costimulatory molecules on the surface of T cells. The first step may also be skipped when the target cells are antigen presenting cells presenting one or more antigens associated with a disease.

Summary of Invention Paragraph:

[0026] Costimulatory molecules on the surface of effector cells may be antigens, fatty acids, lipids, steroids and sugars that can stimulate or costimulate these effector cells' functions to destroy the target cells. Costimulatory molecules include, but are not limited to, CD1 a, CD1b, CD1c, CD2, CD2R, CD3, CD4, CD5, CD6, CD7, CD8, CD9, CD10, CD11a, CD11b, CD11c, CDw12, CD13, CD14, CD15, CD15s, CD16a, CD16b, CDw17, CD18, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD30, CD31, CD32, CD33, CD34, CD35, CD36, CD37, CD38, CD39, CD40, CD41, CD42a, CD42b, CD42c, CD42d, CD43, CD44, CD44R, CD45, CD45RA, CD45RB, CD45RO, CD46, CD47, CD48, CD49a, CD49b, CD49c, CD49d, CD49e, CD49f, CD50, CD51, CD51/61 complex, CD52, CD53, CD54, CD55, CD56, CD57, CD58, CD59, CDw60, CD61, CD62E, CD62L, CD62P, CD63, CD64, CDw65, CD66a, CD66b, CD66c, CD66d, CD66e, CD67, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CDw75, CDw76, CD77, CDw78, CD79a, CD80, CD81, CD82, CD83, CDw84, CD85, CD86, CD87, CD88, CD89, CDw90, CD91, CDw92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD99R, CD100, CDw101, CD102, CD103, CD104, CD105, CD106, CD107a, CD107b, CDw108, CDw109, CD110-CD114, CD115, CDw116, CD117, CD118*, CD119, CD120a, CD120b, CDw121a, CDw121b, CD122, CD123*, CDw124, CD125*, CD126, CDw127, CDw128, CD129, CDw130, LFA-1, LFA-2, LFA-3, VLA-1, VCAM-1, VCAM-2, 4-1BB, cytokine and chemokine receptors. In a preferred embodiment, the bridge molecule has a binding site for CD28 or 4-1BB on the surface of T cells.

Detail Description Paragraph:

[0149] Cellular tumor vaccines can be generated by fusion of tumor cells with antigen processing cells such as activated B cells or dendritic cells. The immunogenicity of fusion tumor vaccine cells can be further enhanced by arming them with antitumor:anti-CD28 bispecific monoclonal antibody (e.g., GP55.times.28, GP95.times.28, GP115.times.28 or GP210.times.28). Without being bound by any theory, applicant proposes that the arming reduces the inhibition of T cell activation by negative signaling from the binding of B7 on fusion cells to CTLA-4 on T cells.